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EXAMINER	
BHAT, NARAYAN KAMESHWAR	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/518,559	OKAMOTO, TADASHI	
	Examiner	Art Unit	
	NARAYAN K. BHAT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-29 and 32-38* is/are pending in the application.

4a) Of the above claim(s) *12,16-23,25,26 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 23, 2009 has been entered.

Status of the Claims

2. This action is in response to papers filed on January 23, 2009.

3. Claims 1, 15, 24 and 27 were amended.

4. Applicant's arguments filed on January 23, 2009 have been thoroughly reviewed and are addressed following claim rejections.

5. Claims 1-5, 8-29 and 32-38 are pending in this application.

6. Claims 12, 16-23, 25-26 and 36 are withdrawn from further consideration in the reply filed on June 18, 2007.

7. Claims 1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38 are under examination.

Amendments to Claims

8. Amendments to the claims 1, 15, 24 and 27 have been reviewed and entered.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Donnell et al (WO 98/20020 published May 14, 1998) in view of Heckman et al (USPN 6,124,099 issued September 26, 2000) and further in view of Marriott et al (Biochemistry international, 1992, 26, 943-951, cited in the IDS of the instant invention).

Regarding claims 1, 15 and 24, O'Donnell et al teaches a method of acquiring data on the mass of a substance fixed on a solid substrate comprising following steps.

O'Donnell et al teaches a photo cleavable linker moiety (i.e., structure including a partial structure) to immobilize nucleic acids (i.e., substance) on the substrate and further teaches that the photocleavable linker are cleaved (i.e., disconnected) by light (pg. 33, lines 12-13, pg. 34, lines 3-4).

O'Donnell et al also teaches irradiating the substance fixed on the substrate with light for inducing the disconnection of the photocleavable linker (i.e., partial structure) to be disconnected by light and analyzing the mass spectrum of the substance which is brought in an unfixed state by disconnecting the partial structure by the irradiation of light (pg. 34 lines 7-21, pg. 84, lines 12-22).

O'Donnell et al also teaches photocleavable linker comprises 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47), which has the structure containing nitrobenzene and further teaches that the nitrobenzyl group as a photocleavable group (pg. 34, lines 3-9), which encompass nitrobenzene is the selected partial structure to be disconnected by the irradiation of light.

O'Donnell et al are silent about the structure containing nitrobenzene is constructed with a compound represented by formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate as defined in the instant specification (paragraph 0115). However a structure containing formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate was known in the art at the time of the claimed invention as taught by Heckman et al.

Heckman et al teaches a photoactive linker succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16) and is the formula II compound as defined in the instant specification (paragraph 0115). Heckman et al also teaches that the succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate linker is an inter strand cross linker, i.e., links RNA and/or DNA strands together and therefore is a bifunctional linker (column 7, lines 49-51 and column 8, lines 13-14). Heckman et al teaches that photoactive linker is used for crosslinking and incorporates into the nucleic acid molecule (column 3, lines 19-29). Heckman et al also teaches that the linker represented by formula II, attaches to the nucleic acid via covalent linkage and has very high long term stability in the dark (column 8, lines 21-27).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the photocleavable linker of O'Donnell et al with the succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate linker of Heckman et al with a reasonable expectation of success.

One having the skill in the art would be motivated to modify the photocleavable linker of O'Donnell et al with the expected benefit of incorporating nitrobenzene derived photo linker forming a covalent bond with a long term stability as taught by Heckman et al (column 8, lines 21-27).

O'Donnell et al in view of Heckman et al are silent about a photo cross-linking agent is also photocleavable. However light mediated chemical bond cleavage was known in the art at the time of the claimed invention was made as taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches the photoclevage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches photoclevage of substance bound to the photocleavable linker occurs through nitrobenzoyl group releasing the substance in a dimeric form into a monomeric form (Fig. 1b). Marriott et al also teaches that light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules provides a simple and effective method to generate concentration jumps of ligands (Fig. 1b, Fig. 3a, pgs. 943, paragraph 1).

As described above, O'Donnell et al, Heckman et al and Marriott et al teaches photoactive linker to link substance. O'Donnell et al and Marriott et al teach photoactive linker is activated by light to disconnect bound substance in the unfixed state by

activation of nitrobenzoyl group (Marriott et al (Fig. 1a) and Marriott et al further teaches photo-cross-linked substance is also photocleaved at the bromobenzyl site to disconnect the biomolecules in the unfixed state (Fig. 1b).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to use the photoactive linker of Heckman et al in the method of O'Donnell et al to fix the substance on the substrate and use the photoclevage method of Marriott et al with the expected benefit of disconnecting the substance from the substrate to increase the concentration of the substance rapidly in unfixed state as taught by Marriott et al (Fig. 3a, pg. 948, lines 9-12), thus increasing the sensitivity of acquiring data from mass of the substance in the method of O'Donnell et al because of increased concentration of the substance at the disconnected site.

Claim 15 recites same steps as recited in instant claim 1. The preamble recites a method of acquiring data on the mass of a bio-related substance. O'Donnell teaches a method of acquiring data on the mass of nucleic acid (i.e., a bio-related substance) on in an array format on a substrate (Fig. 11 and abstract).

Applicant is reminded that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In the instant case, method steps as recited do not require a plurality of bio-related substance fixed on a substrate.

Nonetheless, as described above, O'Donnell et al teaches a plurality of nucleic acids fixed on the substrate.

Claim 24, recites additional limitations of fixing bio-related substance on each matrix. Regarding additional limitation O'Donnell et al teaches 10 to 1000 DNA array spots on the substrate (Example 4, pg. 79, lines 11-16).

Regarding claim 2, O'Donnell et al teaches a method that include a means of analyzing the mass spectrum is matrix assisted laser desorption ionization time-of-flight mass spectrometry (pg. 49, lines 17-22).

Regarding claim 3, O'Donnell et al teaches a laser, i.e., light for inducing the disconnection of the partial structure for the analysis by MALDI-TOF MS (pg. 34, lines 26-28).

Regarding claim 4, O'Donnell et al teaches that the laser beam used for the analysis by MALDI-TOF MS is a nitrogen laser beam (pg. 73, line 7).

Regarding claim 5, O'Donnell et al teaches that the substance fixed on the substrate is nucleic acid (Example 4, pg. 79, lines 13-16).

Regarding claim 8, O'Donnell et al teaches a substrate is a glass substrate (Fig. 7, Step1, pg. 49, lines 1-5) having a primary amino group formed on the surface (Fig. 7, step 2), a thiol (SH) group is bonded to the terminal of the nucleic acid substance, and the amino group and the thiol group are bonded together by a compound (Fig. 7, step 3). O'Donnell et al teach photocleavable linkers comprising 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15) coupling the nucleic acid substance to the substrate. Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate

bifunctional linker (column 3, lines15-16). Marriott et al teaches the photocleavable linker comprising nitrobenzene and succinimide ester (BNBA-SE). Marriott et al further teaches that the amino group and thiol group are bonded together by a linker through a reaction between the amino group and the succinimide ester site of the linker and a reaction between the thiol group and bromobenzyl site of the linker (Fig. 1b, left panel). As described above in rejecting claim 1, use of Heckman linker in place of linker of Marriott et al provide the bonding between the amino group and thiol group as claimed.

Regarding claim 9, O'Donnell et al teaches the formation of a primary amino group on the glass substrate is carried out by using a silane coupling agent having the primary amino group (Fig. 7, pg. 23, lines 14-19).

Regarding claim 10, O'Donnell et al teaches a substrate is a glass substrate (pg. 49, lines 1-5) having a silane coupling agent having thiol group (pg. 65, lines 11-13), which is sulfanil group as defined in the instant specification (paragraph 107). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate bifunctional linker (column 3, lines15-16). Marriott et al teaches the photocleavable linker comprising nitrobenzene and succinimide ester (BNBA-SE). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). Marriott et al further teaches that the amino group is bonded to the terminal of the substance (Fig. 1b, substance –labeled as lysine) and further teaches that thiol group and amino group are bonded together by the linker through a reaction between the thiol group and bromobenzyl site of the linker and a reaction between the amino group and the succinimide ester site of the linker (Fig. 1b, left panel). As described

above in rejecting claim 1, use of Heckman linker in place of linker of Marriott et al provide the bonding between the amino group and thiol group as claimed.

Regarding claim 11, O'Donnell et al teaches the formation of a thiol group on the glass substrate is carried out by using a silane coupling agent having the thiol group (pg. 65, lines 11-13).

Regarding claim 13, O'Donnell et al teaches a substance (matrix substance) for assisting the desorption and ionization of the substance fixed on the substrate is applied to at least a region to be used for the mass spectrometry of the substrate (pg.81, lines 25-29).

Regarding claim 14, O'Donnell et al teaches the thickness of the coating film of the matrix substance is large enough and required for the desorption and ionization of the substance fixed on the substrate (pg. 85, lines 3-29).

Regarding claim 27, O'Donnell et al teaches a method of determining a base sequence of nucleic acid, comprising following steps.

Regarding step 1, O'Donnell et al teaches fixing to a substrate nucleic acid (DNA) complementary to a part or an entire part of a base sequence on a 3'-side from a site desired for analysis of a base sequence of nucleic acid (DNA) desired for analysis of the base sequence as a primer used for performing an enzymatic nucleic acid extension reaction, using the nucleic acid desired for analysis of the base sequence as a template, in a structure containing a partial structure to be disconnected by light on a 5'-side from the complimentary base sequence in the primer (Figs. 18 and 19, pg. 25, lines 24-29 and pg. 26, lines 1-22).

Regarding step 2, O'Donnell et al teaches annealing the nucleic acid desired for analysis of the base sequence to the primer fixed to the substrate at the complementary base sequence portion to form a hybrid (Fig. 18, top left panel).

Regarding step 3, O'Donnell et al teaches performing the enzymatic extension reaction using the nucleic acid desired for analysis of the base sequence as a template, on the substrate where the hybrid is formed, in the presence of appropriate amounts of 4 kinds of 2'-deoxynucleotide triphosphate (dNTP: N is A; adenine, G; guanine, C; cytosine, T; thymine) required for the enzymatic nucleic acid extension reaction and the 4 kinds of 2',3'-dideoxynucleotide triphosphate (ddNTP) as a terminator for an extension reaction (Fig. 18, Top left panel, see the step probe with ddT, pg. 26, lines 1-8).

Regarding step 4, O'Donnell et al teaches removing the template nucleic acid from the substrate where the extension reaction is effected (pg. 37, lines 1-20).

Regarding step 5, O'Donnell et al teaches irradiating a plurality of extension reaction products having different chain lengths including a primer portion fixed to the substrate (Fig. 19). O'Donnell et al also teaches irradiating the substance fixed on the substrate with light for inducing the disconnection of the photocleavable linker (i.e., partial structure) to be disconnected by light and analyzing the mass spectrum of the substance which is brought in an unfixed state by disconnecting the partial structure by the irradiation of light (pg. 34 lines 7-21). O'Donnell et al also teaches analyzing a molecular weight of the extension product disconnected by the irradiation with light by a MALDI-TOF MS method, and clarifying a base sequence of an extension portion of the

extension product based on an increase in a molecular weight from a molecular weight of the primer in the extension product (Fig. 20, pg. 26, lines 24-29).

Regarding step 6, O'Donnell et al teaches analyzing a part or an entire part of the base sequence desired for analysis of nucleic acid desired for analysis of the base sequence, based on the base sequence of the extension portion (Example 6 and 7, pgs. 91-93).

O'Donnell et al also teaches photocleavable linker comprises 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47), which has the structure containing nitrobenzene and further teaches that the nitrobenzyl group as a photocleavable group (pg. 34, lines 3-9), which encompass nitrobenzene is the selected partial structure to be disconnected by the irradiation of light.

O'Donnell et al are silent about the structure containing nitrobenzene is constructed with a compound represented by formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate as defined in the instant specification (paragraph 0115). However a structure containing formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate was known in the art at the time of the claimed invention as taught by Heckman et al.

Heckman et al teaches a photoactive linker succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16) and is the formula II compound as defined in the instant specification (paragraph 0115). Heckman et al also teaches that the succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate linker is an inter strand cross linker, i.e., links RNA and/or DNA strands together and therefore is a

bifunctional linker (column 7, lines 49-51 and column 8, lines 13-14). Heckman et al teaches that photoactive linker is used for crosslinking and incorporates into the nucleic acid molecule (column 3, lines 19-29). Heckman et al also teaches that the linker represented by formula II, attaches to the nucleic acid via covalent linkage and has very high long term stability in the dark (column 8, lines 21-27).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the photocleavable linker of O'Donnell et al with the succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate linker of Heckman et al with a reasonable expectation of success.

One having the skill in the art would be motivated modify the photocleavable linker of O'Donnell et al with the expected benefit of incorporating nitrobenzene derived photo linker forming a covalent bond with a long term stability as taught by Heckman et al (column 8, lines 21-27).

O'Donnell et al in view of Heckman et al are silent about a photo cross-linking agent is also photocleavable. However light mediated chemical bond cleavage was known in the art at the time of the claimed invention was made as taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches the photoclevage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches photoclevage of substance bound to the photocleavable linker occurs through nitrobenzoyl group releasing the substance in a dimeric form into a monomeric form (Fig. 1b). Marriott et al also teaches that light mediated chemical bond cleavage of

nitrobenzyl derivative of biomolecules provides a simple and effective method to generate concentration jumps of ligands (Fig. 1b, Fig. 3a, pgs. 943, paragraph 1).

As described above, O'Donnell et al, Heckman et al and Marriott et al teaches photoactive linker to link substance. O'Donnell et al and Marriott et al teach photoactive linker is activated by light to disconnect bound substance in the unfixed state by activation of nitrobenzoyl group (Marriott et al (Fig. 1a). Heckman et al teaches a photoactive linker comprises nitrobenzyl group and covalently binds to the substance and is stable for long time (column 8, lines 21-27).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to use the photoactive linker of Heckman et al in the method of O'Donnell et al to fix the substance on the substrate and use the photoclevage method of Marriott et al with the expected benefit of disconnecting the substance from the substrate to increase the concentration of the substance rapidly in unfixed state as taught by Marriott et al (Fig. 3a, pg. 948, lines 9-12), thus increasing the sensitivity of acquiring data from mass of the substance in the method of O'Donnell et al.

Regarding claim 28, O'Donnell et al teaches a laser, i.e., light for inducing the disconnection of the partial structure to be disconnected by light is a laser beam used for the analysis by MALDI-TOF MS (pg. 34, lines 26-28),

Regarding claim 29, O'Donnell et al teaches that the laser beam used for the analysis by MALDI-TOF MS is a nitrogen laser beam (pg. 73, line 7).

Regarding claim 32, O'Donnell et al teaches a substrate is a glass substrate (Fig. 7, Step1, pg. 49, lines 1-5) having a primary amino group formed on the surface (Fig. 7, step 2), a thiol (SH) group is bonded to the 5' terminal of the nucleic acid substance, and the amino group and the thiol group are bonded together by a compound (Fig. 7, step 3). O'Donnell et al teach photocleavable linkers comprising 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15) coupling the nucleic acid substance to the substrate. Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate bifunctional linker (column 3, lines15-16). Marriott et al teaches the photocleavable linker comprising nitrobenzene and succinimide ester (BNBA-SE). Marriott et al further teaches that the amino group and thiol group are bonded together by a linker through a reaction between the amino group and the succinimide ester site of the linker and a reaction between the thiol group and bromobenzyl site of the linker (Fig. 1b, left panel). As described above in rejecting claim 1, use of Heckman linker in place of linker of Marriott et al provide the bonding between the amino group and thiol group as claimed.

Regarding claim 33, O'Donnell et al in view of Heckman et al teaches the formation of a primary amino group on the glass substrate is carried out by using a silane coupling agent having the primary amino group (Fig. 7, pg. 23, lines 14-19).

Regarding claim 34, O'Donnell et al teaches a substrate is a glass substrate (pg. 49, lines 1-5) having a silane coupling agent having thiol group (pg. 65, lines 11-13), which is sulfanil group as defined in the instant specification (paragraph 107). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate bifunctional linker (column 3, lines15-16). Marriott et al teaches the photocleavable

linker comprising nitrobenzene and succinimide ester (BNBA-SE). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). Marriott et al further teaches that the amino group is bonded to the terminal of the substance (Fig. 1b, substance –labeled as lysine) and further teaches that thiol group and amino group are bonded together by the linker through a reaction between the thiol group and bromobenzyl site of the linker and a reaction between the amino group and the succinimide ester site of the linker (Fig. 1b, left panel). As described above in rejecting claim 1, use of Heckman linker in place of linker of Marriott et al provide the bonding between the amino group and thiol group as claimed.

Regarding claim 35, O'Donnell et al teaches a substrate is a glass substrate (pg. 49, lines 1-5) having a silane coupling agent having thiol group (pg. 65, lines 11-13), which is sulfanil group as defined in the instant specification (paragraph 107).

Regarding claim 37, O'Donnell et al teaches a Thermo sequenase, an enzyme used for the extension reaction has heat resisting property (Fig. 19, pg. 92, lines1-3).

Regarding claim 38, O'Donnell et al teaches a method wherein the substrate to which the primer is fixed is in a form of a nucleic acid chip in which a plurality of primer nucleic acids are placed in a matrix in the process (Fig. 19, pg. 83, lines 1-15) a part or an entire part of the primer nucleic acid is subjected to an enzymatic nucleic acid extension reaction together with the template thereof on the nucleic acid chip, and in the process (4), the matrix portion subjected to the extension reaction is analyzed by the MALDI-TOF MS method (pg. 83, lines 16-24).

Response to remarks from the Applicants

Rejections under 35 U.S.C. § 103(a)

11. Applicant's arguments filed January 23, 2009 with respect to claims 1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38 as being unpatentable over O'Donnell et al in view of Heckman et al and further in view of Marriott et al (Remarks, pgs. 10 -15) have been fully considered but are not persuasive for the following reasons.

Note: Applicant's arguments filed on January 23, 2009 are identical to the arguments filed after the final action on December 2, 2008. An advisory action was mailed on January 26, 2009 in response to the Applicant's arguments filed on December 2, 2008. Response to Applicant's arguments filed on January 23, 2009 is listed below.

Applicants argue that O'Donnell et al alone or in combination with Heckman and Marriott does not disclose each and every step of the claimed method (Remarks, pg. 11, paragraph 2, and lines 1-2). This argument is not persuasive because as described above in section 10, O'Donnell et al, Heckman et al and Marriott et al teaches method steps as claimed.

Applicants further argue that the compound analyzed by mass spectroscopy in O'Donnell et al is not the immobilized DNA strand but the annealed strand, which detaches under mass spectroscopic conditions and the Examiner is erroneous in alleging that 'O'Donnell teaches analyzing the mass spectrum of the substance which was brought in an unfixed state by disconnecting the partial structure by the irradiation

of light (Remarks, pg. 11, paragraph 2). These arguments are not persuasive for the following reasons.

a) As described above in section 10, O'Donnell et al explicitly teaches structure to be disconnected by light (i.e., photocleavable linkers) to fix nucleic acids on the substrate and irradiating the fixed nucleic acids on the substrate with light for inducing the disconnection and analyzing the mass spectrum (pg. 33, lines 12-17, pg. 34, lines 3-21).

b) It is noted that O'Donnell et al teaches different embodiments comprising mass spectra of the extended nucleic acids as well as fixed nucleic acids on the substrate (pg. 34, lines 19-21). Since O'Donnell et al teaches the mass spectra of the photo cleaved nucleic acid Applicant's arguments are not persuasive.

Applicant further argues that the Examiner is erroneous in alleging that O'Donnell et al teaches irradiating the substance fixed on the substrate with laser and analyzing the mass spectrum of the substance which is brought in an unfixed state by disconnecting the partial structure by the irradiation of light (Remarks, pg. 11, paragraph 2, pg. 12 and paragraph 1). This argument is not persuasive because instant claims are rejected using combination of references. The structure represented by formula II is taught by Heckman et al and Marriot et al teaches to photo-cleaving of photo-cross-linked substance to release the substance in a unfixed state.

Applicant further reiterates the argument that the combination of O'Donnell et al Heckman et al and Marriott et al does not make obvious the claimed invention and further argues that O'Donnell does not teach the formula II compound (Remarks pg. 12,

paragraphs 2 and 3). These arguments are not persuasive because Applicant is attacking references individually to make the rejection non-obvious. Furthermore courts have ruled that arguments attacking individual references are not persuasive when the rejections are based on combinations of references (See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)).

In the instant case, as described above in section 10, O'Donnell et al teaches photocleavable linkers comprising nitrobenzene group to fix the substance on the substrate and disconnect the substance by irradiation of light. Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate compound, which is defined as Formula II compound in the instant specification (paragraph 0115) and asserted by the Applicant (Applicant's response, April 21, 2008). Heckman et al further teaches that the formula II compound is a bifunctional linker because it links two RNA and/or DNA strands together. Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link substance and further teaches photo-cross-linked substance is also photocleaved at the bromobenzyl site to disconnect the substance in the unfixed state.

The recent Supreme Court decision in KSR Intl. Co. v. Teleflex Inc. rejected the rigid approach of applying a strict TSM test as the sole basis for obviousness and that the analysis for obviousness need not seek out precise teachings directed to the specific subject matter of a claim. Further the decision set forth that the analysis can take into account the inferences and creative steps that a person of ordinary skill in the

art could employ and that a person of ordinary skill in the art is also a person of ordinary creativity, not an automaton. Furthermore, the decision set forth that a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.

Since method steps and formula II compound were known in the art at the time of the claimed invention was made and Heckman et al and Marriott et al provide teachings, suggestions and motivations to use the formula II compound in place of photocleavable linker of O'Donnell et al, Applicant's arguments are not persuasive.

Applicants further argue that Heckman et al teaches cross linking occurs at UV wavelength > 300 nm, while photo induced cleavage occurs at around 350 nm and skilled artisan would be perplexed about what would happen under UV irradiation as two alleged photoreactions would be competing against each other (Remarks, pg. 12, paragraph 2, pg. 13, paragraph 1). These arguments are not persuasive because Heckman et al teaches that the photo-cross-linking occurs at 312 nm (column 12, line 22). Marriott et al teaches photo-cross-linked product is photo-cleaved at 320-400 nm (Fig. 1b). Therefore skilled artisans won't be perplexed about photocross linking and photo cleavage competing against each other because they occur at two different wavelengths. An artisan would choose appropriate wave length of light to disconnect the substance from the substrate as taught by Marriott et al. Since photo-linkers of O'Donnell et al, Heckman et al and Marriot et al comprise nitrobenzene structure and Marriott et al teaches cleaving of photo-cross-linked substance with light to disconnect substance in unfixed state, Applicants arguments are not persuasive.

Applicants further argues that the Examiner must view cited art as a whole and cannot ignore the teachings of Heckman et al and further cites MPEP 2143.01, which clearly states the proposed modification of the prior art cannot change the principle of operation of the primary references or the references inoperable for its intended use (Remarks, pg. 5, paragraph 3). This argument is not persuasive because, MPEP 2143.01 citation is for suggestion or motivation to modify the references. MPEP 2141.02 provides guidance for "Differences between Prior Art and Claimed Invention". As described above, Heckman's teaching of formula II compound as a photocross linker does not change the invention of O'Donnell et al, because it is known in the art that photo-cross-linked product is also photo-cleavable as explicitly taught by Marriott et al.

Applicant further argues that merely because the compound has a nitrobenzoyl group does not make it a compound suitable in the process taught by O'Donnell et al (Remarks, pg. 12, paragraph 3). This argument is not persuasive because, arguments of counsel are not found persuasive in the absence of factual showing. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

In the instant case, Applicant has asserted that O'Donnell et al teaches the mass spectra of the immobilized substance on the substrate and Heckman et al teaches the formula II compound (Remarks, April 21, 2008). Marriott et al teaches photo-cross-linked product is also photo-cleavable at the bromobenzyl site of the structure containing nitrobenzene and therefore arguments of counsel are not persuasive.

Applicant further argues that O'Donnell et al, Heckman et al and Marriott et al fail to teach, suggest or disclose method as claimed (Remarks, pg. 14, paragraph 3). This argument is not persuasive because Applicant has not traversed the teachings and suggestions and motivations of Heckman et al incorporating formula II compound in place of photocleavable linker of O'Donnell et al. Also, Applicants have not provided any support evidence why formula II compound would not work in fixing substance on the substrate and disconnecting the substance from the substrate by light in the method of O'Donnell et al in view of teachings of Marriott et al. As described above in section 10, O'Donnell et al, Heckman et al and Marriott et al teach method steps as recited in instant claims, Applicant's arguments regarding failing to teach, suggest or disclose method as claimed by O'Donnell et al, Heckman et al and Marriott et al are not persuasive.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on (571)-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Narayan K. Bhat/

Examiner, Art Unit 1634

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/Ram R. Shukla/

Supervisory Patent Examiner, Art Unit 1634